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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/067,146 | 02/04/2002 | Frederick P. Siegal | 10034-004 | 7266 |

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| EXAMINER | |
|---|---|
| KAUSHAL, SUMESH | |
| ART UNIT | PAPER NUMBER |
| 1636 | |

DATE MAILED: 08/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/067,146 | SIEGAL ET AL. | |
| | Examiner | Art Unit | |
| | Sumesh Kaushal Ph.D. | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 May 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *11,15 and 20-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,15 and 20-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Applicant's response filed on 5/17/04 has been acknowledged.

Claims 1-10, 12-14 and 16-19 are canceled

Claims 20-35 are newly filed claims

Claims 11, 15 and 20-35 are pending and are examined in this office action

Applicants are required to follow Amendment Practice under revised 37 CFR §1.121. The fax phone numbers for the organization where this application or proceeding is assigned is **703-872-9306**.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The references cited herein are of record in a prior Office action.

### *Claim Rejections - 35 USC § 112*

Claims 11, 15 and 20-35 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

**Nature of Invention:**

Invention relates to a method of monitoring the progression of a disease or disorder resulting from HIV infection in a patient by measuring the number of pDC2 cells in lymphoid or blood sample obtained from the patient as compared to a control sample or a previously determined reference range.

**Breadth of Claims and Guidance Provided in the Specification**

The scope of the invention as claimed encompasses a method of monitoring the progression of any disease or disorder (*pathogenic or non-pathogenic, genetic or environmental*) resulting from HIV infection in a patient by measuring number of pDC2 cells obtained from lymphoid tissue or blood sample of a HIV patient and comparing it to a control sample. At best the specification only discloses evaluation of IFN-α production by total PBMCs or pDC2-depleted, pDC2-enriched mononuclear cells (pages 30-32). The specification further teaches a method of evaluating the number of pCD2-interferon-producing dendritic cells by cell sorting techniques (fig-1 and 2). The specification further disclosed statistical correlation among IFN-α generation, CD4 T-cell counts and viral burden in HIV patients (page 34, sec.8.2; page 40 table-1). However, the specification as filed fails to establish any correlation between the number of pCD2-interferon-producing dendritic cells and the progression of any disease or disorder resulting from HIV infection. Similarly the specification fails to establish the reference range (control sample) for pDC2 cells especially in context with a disease or disordered resulting form HIV infection, wherein the pDC2 cells has been obtained from lymphoid tissue or blood sample obtained from the normal subject and HIV patient.

**State of Art and Predictability**

Interferons are the cytokines produced by virus-infected cells that enable neighboring cells to resist virus infection. IFN-α (leukocyte IFN) and IFN-β (fibroblast IFN), the two type 1 antiviral IFNs, are distinct from type 2 IFN-γ produced by effector T cells. Specialized leukocytes, the "natural IFN-producing cells" (NIPCs), were shown to be the chief IFN-γ producers in response to enveloped viruses, bacteria, and tumor cells. IPCs express CD4 and major histocompatibility complex (MHC) class II, but lack hematopoietic-lineage markers. Therefore the nature of IPCs, whether they represent dendritic cells or cells of a distinct lineage has been controversial. There is a progressive loss of CD4+ T lymphocytes and functional IPCs during human immunodeficiency virus (HIV) infection. Preservation of IPCs is associated with protection from opportunistic infections, suggesting the importance of IPCs in the host defense (Siegal et al, Science 284:1835-1837, 1999, *ref. of record, see page 1835*).

Furthermore, increased frequency and severity of infections in the elderly have been taken as indicative of declining immune function. Dendritic cells (DCs), the most important antigen-presenting cells, play a central role in initiating and modulating immune responses. One type, DC2, arises from precursor plasmacytoid DCs (pDCs), a rare population of circulating blood cells, whose hallmark function is rapid and copious production of interferon- (IFN-α) upon microbial challenge. However there is a significant decrease of the circulating pDCs during ageing in healthy adult humans (Shodell et al Scand J. Imunol 56:518-521, 2002 see page 518). Furthermore the cellular identity of NIPC is the most important issue in the enumeration of NIPC in a particular disease. For example it is important establish whether these cells represent a unique lineage or do they belong to an already defined lineage of cells such as dendritic cells. The developmental pathway of NIPC has not been well characterized. The cellular distribution of NIPC is also not known, since appropriate tissue studies have not been performed to determine whether the cells are able to move out of periphery and into tissues. Clearly most significant impairment to studies of IFN-α system in human peripheral blood remains the inability to identify the unique NIPC (Fitzgerald-Bocarsly et al Pharmac. Ther. 60:39-62, 1993, *ref. of record see page 56 sec.7*).

***Response to arguments***

The applicant argues that the claims as amended are directed only to diseases or disorders resulting from HIV infection, and involve measuring pDC2 cells in blood or lymphoid tissues. The applicant argues that the specification establishes that production of IFN-α is closely correlated with pCD2 cells, such that any measurement of IFN-α levels would be expected to be a good measurement of the number of pCD2 cells present. The applicant argues that the claims are fully enabled, since the skilled artisan would understand that the disclosure establishes a correlation between disorders resulting from HIV infection and pDC2 cell occurrence in blood or lymphoid tissue. The applicant argues that a control or reference range for any particular population can be effected without undue experimentation by the skilled artisan, simply by quantifying pDC2 cells in a sufficient number of healthy, non-infected individuals.

However, applicant's arguments are found NOT persuasive because the disclosure "shall inform how to use, not how to find out how to use for themselves." See In re Gardner 475 F.2d 1389, 177 USPQ 396 (CCPA 1973). The specification as filed fails to establish any correlation between the number of pCD2-interferon-producing dendritic cells and the progression of any disease or disorder resulting from HIV infection. The specification fails to establish the reference range (control sample) for pDC2 cells in context with a disease or disordered resulting form HIV infection, wherein the pDC2 cells has been obtained from lymphoid tissue or blood sample of a normal subject or an HIV patient. The earlier office action clearly provided the evidence that there is a significant decrease of the circulating pDCs during ageing in healthy adult humans. In addition loss of pDC IFN-a generation by blood MNC attributable not only to declining pDC number but also to the reduction in IFN generated per pDC (Shodell et al Scand J. Imunol 56:518-521, 2002 see page 518, 521). Therefore it is highly unpredictable to predict the number of pDC2 (as claimed) by evaluating the levels of IFN-$\alpha$ produced in a sample. In addition the cellular identity of IPC is the most important issue in the enumeration of IPC in a particular disease. For example it is important to establish whether these cells represent a unique lineage or do they belong to an already defined lineage of cells such as dendritic cells. In the instant case the scope of pCD2 cells as claimed encompasses a dendritic cells with any phenotype, whereas the instant specification only identify pCD2 cells as cells that are $CD4^+$, $CD3^-$, $CD11c^-$. Furthermore the cellular distribution of pCD2 is not known, since appropriate tissue studies have not been performed to determine whether the cells are able to move out of periphery and into tissues. Therefore the identification of pCD2 is considered germane in evaluating the number of pCD2 cells in health or a disease resulting form HIV infection.

In addition monitoring the progression of any disease or disorder resulting from HIV-infection by evaluating the number of pDC2 in a sample obtained form a bllodd or any lymphoid tissue of a subject having HIV infection is not considered routine in the art and without sufficient guidance to a specific disease/disorder and its correlation to number of pDC2 cells eliciting a specific phenotype, the experimentation left to those

skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). Therefore considering the state of the art and limited amount of guidance provided in the instant application one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

## Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sumesh Kaushal Ph.D. whose telephone number is 571-272-0769. The examiner can normally be reached on Mon-Fri. from 9AM-5PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yucel Irem Ph.D. can be reached on 571-272-0781.

*Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to* ***(571) 272-0547.***

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199. The fax phone number for the organization where this application or proceeding is assigned is **703-872-9306.**

Sumesh Kaushal
Examiner GAU 1636

JEFFREY FREDMAN
PRIMARY EXAMINER
8/3/04